Remarks

Claims 16-37 are pending in the application and currently stand rejected. Claims 16-30 and 37 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled. With entry of this amendment, Applicants have canceled claims 1-15, 19, and 29-37, amended claims 16, 17, and 18, and added claims 38-46. In particular, Applicants note that claim 16, the only independent claim currently pending, has been amended to (1) specify the type of cells which are contacted according to the methods of the invention, and (2) to recite the DNA binding and transcription suppression domains of the fusion polypeptide utilized in the claimed methods. Applicants have amended their claims without prejudice and expressly reserve the right to pursue claims of equal or greater scope in this application or in a related application.

Support for the claim amendments can be found in the specification as originally filed and in the claims as originally filed. No new matter has been added. For the reasons set forth herein, each of the rejections is overcome.

I. Response to Claim Rejections under 35 U.S.C. § 112, First Paragraph

A. Summary of Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 16-30 and 37 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled. The Office Action alleges that the claims are not enabled for several reasons which can be summarized as follows: (1) the breadth of the claims is not commensurate with the specification; (2) cancer may arise from numerous molecular changes; (3) "corrective cancer gene therapy" requires correction of "genetic defect in all the cancer cells;" and (4) gene delivery is considered a "highly experimental" and unpredictable area of research. *See* Office Action at pages 3-4. The Office Action also alleges that the specification does not provide sufficient direction or guidance to one of skill in the art to practice *any* of Applicants' claims. *See, e.g.*, Office Action at page 3.

Specifically, the Examiner states that only *in vitro* claims are supported by Applicants' disclosure. *See id.*

As discussed in the Remarks section above, Applicants have substantially amended the pending claims. Applicants' amended claims do not read on "corrective cancer therapy" which require the correction of "genetic defects in all cells," but are drawn instead to methods for suppressing the hyperproliferative growth of arterial cells associated with conditions such as restenosis. Applicants have also amended the claims to recite the administration of a defined set of nucleic acid compositions. Applicants respectfully submit that the amendments to the claims presented here render the Examiner's arguments in the Office Action moot. Applicants present the following arguments and evidence in support of the enablement of the amended claims.

B. Applicants do not claim a method for curing cancer or a method for permanently destroying every cancer cell in a patient

Before passing on the allowability of claims under any section of 35 U.S.C., an Examiner is first required to give the claims their "broadest *reasonable* interpretation." *See* MPEP § 2111. In the Office Action, the Examiner evaluated Applicants' claims as if they were drawn to methods of *curing* cancer or eliminating tumors without any of the risks associated with FDA-approved cancer therapies. For example, the Examiner alleges on page 3 of the Office Action that "corrective cancer gene therapy requires correction of genetic defect[s] in all the cancer cells . . ." The Examiner then cites an article by W. French Anderson (Nature 392:25-30 (1998)) in support of the proposition that "gene therapy" is "highly experimental" and "difficult to predict." *Id.*

Whether the term "gene therapy" is correctly construed to encompass only (or even primarily) methods for *permanently eliminating* every last tumorous cell from a patient is moot because Applicants claims do *not* recite the term "gene therapy," nor do they recite a method for treating cancer. Instead, each of Applicants' pending claims is drawn to a method of *suppressing* the growth of *hyperproliferative arterial cells* using

Applicant's novel vectors which encode Applicant's novel polypeptides. The vast majority of Applicants' pending claims recite additional limitations. Therefore, insofar as Applicants do not *claim* to have invented the field of "gene therapy," Applicants submit that they need not enable the entire field of "gene therapy."

Moreover, as stated in MPEP 2164.08, the scope of enablement need only bear a "reasonable correlation" to the scope of the claims. *See, e.g., In re Fisher*, 427 F.2d 833, 839 (CCPA 1970); *see also Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (a claim may encompass inoperative embodiments and still meet the enablement requirement). It is respectfully submitted that the methods described in Applicants' disclosure bear a reasonable correlation to the methods recited in the amended claims. Therefore, particularly in light of the data described in the specification and acknowledged in the Office Action, Applicants respectfully submit that the pending claims satisfy the enablement requirement.

C. The references cited in the Office Action do not accurately reflect the state of the relevant art or the skill of those in the relevant art

1. *Wands* factors, predictability, and the state of the relevant art

The Federal Circuit has addressed the factual premises of the enablement analysis for biological processes, explaining that determination of whether the requisite amount of experimentation is undue may include consideration of:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

See In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). With respect to the level of skill in the art, Applicants take issue with the Examiner's assertion that, at the time Applicants filed their application, the techniques involved were considered a "highly experimental area of research." *See* Office Action at page 4. As discussed above, Applicants do not claim to have invented "gene therapy," nor do Applicants contend that the scope of their

claims includes the universe of all "gene therapy" applications. Applicants respectfully submit that the relevant art to consider is the art of introducing into targeted cells a vector encoding DNA binding proteins which affect transcription, such that the vectors are incorporated into at least a portion of the targeted cells. At the time of Applicants' filing, there were many highly skilled practitioners capable of following Applicants' disclosed protocols and performing the routine experimentation -- manipulation of vectors, identification of targetable cells, *etc.* -- which contributes to the enablement of Applicants' claimed methods.

With respect to the use of nucleic acids for delivering and expressing genes which attenuate the hyperproliferative growth of cells, this technology was in use several years before Applicants' priority date. For example, as early as 1994, the effective peritumoral delivery of adenoviruses encoding p53 was demonstrated by Wills et al. (*Human Gene Therapy, 5*:1079, 1081 (1994)) (copy enclosed). Also, Schuler et al. (*Human Gene Therapy, 9*:2075-2082 (1998)) (copy enclosed) report the successful intratumoral administration (*see, e.g.*, p. 2077) of adenoviruses expressing heterologous genes, and Nielsen *et al.* (*Cancer Research* 59:5896-5901 (1999)) (copy enclosed) provide examples of the effective intraperitoneal administration of such vectors (*see, e.g.*, p. 5897). Applicants' specification teaches one skilled in the art how to make and use adenoviral vectors and a variety of promoters, and these vectors and promoters are explicitly recited in Applicants' claims.

Because antibodies and antisense nucleotides against Rb and other tumor suppressors are well-known and widely available, the determination of cells that are deficient in tumor suppressor activity is also routine. For example, Wills et al. (1994) *supra* discuss the detection of p53 at page 1081. The Cooper *et al.* reference (*Oncogenes*, (1990)) cited by the Examiner is particularly relevant because Cooper teaches that the introduction of a functional normal Rb gene reverses the tumorigenicity of retinoblastoma cells lines in which the endogenous gene had been deleted (*see*, page 133, lines 17-19 of Cooper). Thus, the necessary techniques were known to the artisan at the

time the present application was filed and undue experimentation would not be necessary to evaluate the status of Rb in cells in order to practice embodiments of the claimed invention which include the step of treating cells which are deficient in functional Rb expression.

With respect to the breadth of Applicant's disclosure, Applicant's specification provides one of skill in the art with more than adequate instruction to make and use the vectors of the present invention without undue experimentation. For example, a description of the desirable components of useful vectors for practicing the claimed methods is described on page 9, lines 13-28 of the specification. Promoters useful in the present invention are discussed on page 9, lines 29-38 and page 10, lines 1-13 of the specification. In addition, numerous examples of a number of suitable promoters are given on page 10, lines 14-36 and on pages 11-12 of the specification. At the time of filing, one of skill in the art would be familiar with the commonly used molecular biology techniques useful for constructing vectors of the present invention following the guidelines provided in the specification, as well as the commonly used techniques for delivery of the vectors (*e.g.*, locoregional administration and direct injection techniques, as discussed on page 16 of the specification; vector-coated stents, as described on page 19).

In addition, Applicants attach to this Amendment a copy of a paper by Wills et al. (*Gene Therapy*, *8*:1847-54 (2001) which demonstrates that Applicants' claimed methods and novel compositions have been successfully used to specifically suppress the growth of smooth muscle cells *in vitro* (*see*, *e.g.*, Figs. 2 and 4 on pages 1849 and 1851, respectively), and to attenuate the hyperproliferative growth of arterial cells *in vivo* (*i.e.*, neointima; *see*, *e.g.*, Figs. 5 and 6). Specifically, Fig. 2 of Wells *et al.* (2001) shows that expression from nucleic acid vectors such as those described in Applicants' specification can be directed to specific cell types by using a tissue-specific promoter. Figure 4 (as well as Table 1) shows that the expression of the E2F/Rb fusion protein described in Applicants' specification can specifically suppress the growth of

smooth muscle cells *in vitro*. Figure 6 shows that in an *in vivo* animal model for restenosis, an adenoviral vector driving expression of Applicants' novel fusion polypeptide from a smooth muscle specific promoter is capable of inhibiting neointima formation *in vivo* by 37% relative to a control vector (*see* page 1849). The results of Wills *et al.* (2001), particularly in light of Applicants' teaching in the specification, unequivocally establish that Applicants' methods are fully enabled by Applicants' specification. As such, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

2. The W. French Anderson article cited in the Office Action does not accurately reflect the relevant state of the art

On page 4 of the Office Action, the Examiner cites an article by Dr. W. French Anderson (1998) for the proposition that Applicants' claimed methods are "gene therapy" and thus belong to a "highly experimental" and unpredictable area of research. As discussed above, Applicants submit that this characterization of their claims is overbroad. Moreover, Applicants respectfully submit that the Anderson article does not accurately reflect the state of the art at the time of Applicants' filing, nor does it accurately reflect Dr. Anderson's owns views on the subject.

With respect to Dr. Anderson's opinion of the state of the art with respect to "gene therapy" methods, the Examiner should take notice of the fact that the opinions in Dr. Anderson's magazine article are strikingly at odds with the position he took before the PTO with respect to various patent applications on which he appears as an inventor.[1] For example, Dr. Anderson appears as an inventor on U.S. Patent No. 6,503,501, which claims priority to an application filed November 9, 1992. The patent issued January 7, 2003. The issued method claims appear to encompass the use of retroviruses for *in vivo* "gene therapy" and, in fact, the specification of the patent clearly states that "an object of the present invention [is] to provide gene therapy by introduction of a vector particle,

such as, for example, a retroviral vector particle, directly into a desired target cell of a patient." The specification does not disclose a single Example of *in vivo* efficacy. Nowhere in the patent (and presumably nowhere in the prosecution history) does Dr. Anderson candidly disparage the field of gene therapy as he allegedly does in the *Nature* article cited by the Examiner.[2] Applicants submit once again that Dr. Anderson's statements and actions before the PTO are more relevant to his beliefs with respect to the enablement issues highlighted by the Examiner than are Dr. Anderson's statements in a journal article summarizing the clinical and commercial "success" of "gene therapy."

3. Clinical data is not required to show enablement of treatment method claims

For the record, Applicants respectfully remind the Examiner that they need ***not*** demonstrate the FDA-required degree of clinical efficacy or even any clinical efficacy at all to meet the enablement requirement. *See In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). The clinical certainty required to treat a human subject is *not* the standard for an enabling disclosure.[3]

Moreover, the expression of a tumor suppressor protein in humans is not recognized by those of skill in the art as a useless and dangerous exercise. For example, Nielsen et al. in *Cancer Gene Therapy, 5(1)*:52-63 (1998) (copy enclosed), note that several studies report expression of tumor suppressor genes (*see, e.g.*, p. 54) accompanied by little or no detrimental treatment-related effects (*see, e.g.*, p. 59). Likewise, Schuler et al. (1998) *supra* report expression of tumor suppressor gene RNA and only mild to moderate toxicity (see, *e.g.*, pp. 2077-2078). Moreover, Reid et al. (*Cancer Gene Therapy, 9*:979-986 (2002)) (copy enclosed) note that several groups have described

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[1] Dr. Anderson appears as an inventor on at least ten issued gene therapy patents, at least several of which claim priority to applications filed before Applicants' application.
[2] Applicants note that under 37 CFR 1.56 Dr. Anderson had a duty to disclose information *believed to be* material to the patentability of the invention, including information regarding the unpredictability of the art.
[3] To quote Supervisory Patent Examiner Karen Hauda, "We DO NOT Require Clinical Data." (emphasis in original) *See,* the USPTO's "Gene Therapy: Overcoming Enablement Rejections" PowerPoint training materials.

tumor suppressor gene expression (in this instance, p53) with an acceptable toxicity profile, including human trials (*see, e.g.*, abstract).

D. Applicants claims are commensurate with the disclosure in the specification and can be practiced without undue experimentation

In conclusion, the Examiner has not met the burden of providing acceptable objective evidence or reasoning that calls into question the enablement of Applicants' *claimed* invention. In the Office Action, the Examiner relies on selected references to argue that gene therapy as a field is not enabled. The weight of the evidence, when considered as a whole, indicates that those of skill in the art consider certain aspects of gene therapy to have practical utility and efficacy. Indeed, as discussed herein, the Patent Office has agreed in numerous instances indistinguishable, at least in terms of the evidence presented, from the circumstances here. For all of the forgoing reasons, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

CONCLUSION

In view of the foregoing Amendment, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5004.

Respectfully submitted,

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